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PATENT & TRADEMARK OFFICE

PATENT
Docket No. 030557

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: K. J. Puttlitz	:	
Art Unit: 1621	:	
In re application of: Gladysz, et al.	:	RECOVERY METHOD FOR CATALYSTS, REAGENTS AND CO-PRODUCTS
Serial No.: 10/664,105	:	
Filed: September 17, 2003	:	

DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

We, John A. Gladysz, Marc Wende and Dennis P. Curran hereby declare and state as follows:

1. We are the listed inventors of U.S. Application Serial No. 10/664,105 ("subject application") and of the subject matter described and claimed therein, which claims priority to United States Provisional Application No. 60/411,439 filed September 17, 2002.

2. The subject application discloses and claims methods for conducting a chemical reaction using a fluorous compound in a non-fluorous medium, in the presence of a solid adsorbant containing a fluorous domain and at least one chemical reactant.

3. The methods described and claimed in the subject application were conceived and reduced to practice prior to 30 May 2001, as evidenced by the following:

a. Prior to 30 May 2001, and specifically during the period 1 March 2001 through 30 April 2001, co-inventors John A. Gladysz and Marc Wende, conceptualized the initial idea of using a fluorous support to aid catalyst recovery in the reactions as described in the paper Wende, M.; Meier, R.; Gladysz, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 11490, ("the JACS paper") which was submitted for publication on 11 June 2001. Appendix A contains a copy of the JACS paper which shows receipt of the JACS paper on 12 June 2001. During the period from 1 March 2001 through 29 May 2001, the claimed process was initially reduced to practice using Teflon® shavings as described in the JACS paper. All experiments described in the JACS paper were completed prior to 30 May 2001.

b. As further evidence of reduction to practice prior to 30 May 2001, Appendix B contains two laboratory notebook pages from the Notebook of co-inventor Marc Wende describing successful reduction to practice of the claimed invention. In particular, the notebook pages describe either Teflon or Teflon "Stückchen" (little pieces) additives to aid the recovery of fluorous phosphine catalysts following addition reactions involving alcohols and methyl propiolate. The experiments described on these notebook pages were performed prior to 30 May 2001.

c. Also, these ideas and the experimental design were discussed at a group meeting by Mr. Wende on 21 March 2001. A copy of the group meeting schedule showing Mr. Wende's scheduled discussion on 21 March 2001 is submitted in Appendix C.

4. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further

that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

11-April 2008 Date	John A. Gladysz
Date	Marc Wende
Date	Dennis P. Curran

that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date	John A. Gladysz
04/14/2008 Date	Marc Wende
Date	Dennis P. Curran

that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date	John A. Gladysz
Date	Marc Wende
4/10/08 Date	Dennis P. Curran

APPENDIX A

Fluorous Catalysis without Fluorous Solvents: A Friendlier Catalyst Recovery/Recycling Protocol Based upon Thermomorphic Properties and Liquid/Solid Phase Separation

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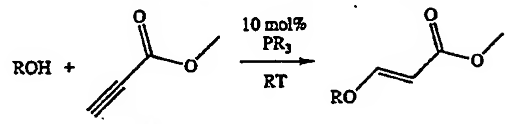
Received June 12, 2001

Over the last 6 years, many new catalysts with high affinities for fluorocarbon (fluorous) solvents have been synthesized.[1,2] This has been prompted by the development of "fluorous biphase catalysis",[1a] which as most often practiced exploits the markedly temperature-dependent miscibilities of organic and fluorous solvents. At room temperature, most combinations give two phases.[3] However, with moderate heating, one phase is obtained. Reactions can be catalyzed under monophasic conditions at the high-temperature limit and the products and catalyst separated under biphasic conditions at the low-temperature limit.

No catalyst recovery method is without potential drawbacks.[4] Accordingly, the fluorous solvent requirement in this protocol has mobilized a vocal contingent of nay-sayers, the major objections from which involve cost and environmental persistence.[3] However, a way to eliminate any such problems has been overlooked. High fluorous-phase affinities are achieved by appending a number of "pony tails" $(CH_2)_m(CF_2)_{n-1}CF_3$ (typically $m = 0-3$, $n = 6-10$) to the catalyst, often giving a low-melting solid. What has not been appreciated is that the same factors that give highly temperature-dependent organic/fluorous *liquid/liquid* phase miscibilities can also give highly temperature-dependent organic/fluorous *liquid/solid* phase miscibilities (e.g., solubilities). In less conceptual terms, as we gained more and more experience with pony-tail-containing fluorous compounds in our laboratory, we began to notice marked increases in solubilities with temperature, particularly near melting points.

A case in point is the easily prepared fluorous phosphine $P((CH_2)_2(CF_2)_7CF_3)_3$ (1), which melts at 47 °C.[5] As part of a study involving many related phosphines,[5,6] we began to probe various types of phosphine-catalyzed organic reactions already in the literature.[7,8] The addition of alcohols 2 to methyl propiolate (3) shown in Chart 1 was selected for emphasis.[8] Good yields of addition products 4 were obtained at room temperature with both a previously reported catalyst system, $P(n\text{-}Bu)_3$ in CH_2Cl_2, and 1 in $CF_3C_6H_5$. The latter solvent was selected for its ability to dissolve both fluorous and nonfluorous compounds.[9] The mechanism is believed to involve initial 1,4-addition of the phosphine to give a zwitterionic allenolate, which then deprotonates the alcohol.[8a] An alkoxide addition/phosphine elimination sequence gives the product and regenerates the catalyst. Reactions should be slower in less polar solvents, consistent with the data in Chart 1. $P(n\text{-}Bu)_3$ was also an effective catalyst in $CF_3C_6H_5$ and gave faster rates than 1, consistent with its greater basicity and nucleophilicity.[6d]

Chart 1. Phosphine-Catalyzed Addition Reaction



2 3 4

$1 = P((CH_2)_2(CF_2)_7CF_3)_3$

	ROH (0.9 equiv)	Catalyst	Solvent	Yield (%)	Time (h)
2a	$PhCH_2OH$	1	$CF_3C_6H_5$	90 [a]	24
				95 [a]	96
		$P(n\text{-}Bu)_3$	CH_2Cl_2	72 [b]	0.5
2b	Ph_2CHOH	1	$CF_3C_6H_5$	78 [a]	48
		$P(n\text{-}Bu)_3$	CH_2Cl_2	85 [b]	0.5
2c	$PhCH(CH_3)OH$	1	$CF_3C_6H_5$	81 [a]	24
		$P(n\text{-}Bu)_3$	CH_2Cl_2	89 [b]	0.5
2d	$CH_3(CH_2)_7OH$	1	$CF_3C_6H_5$	86 [a]	48
		$P(n\text{-}Bu)_3$	CH_2Cl_2	77 [b]	0.5

[a] GC yield (vs internal standard); starting concentrations: 0.3 M (2b) or 0.5 M (2a, c, d). [b] Isolated yield after Kugelrohr distillation (≥98% purity); starting concentrations: 1.5 M (2b) or 1.0 M (2a, c, d).

We were able to recycle catalyst 1 using standard liquid biphase (e.g., $CF_3C_6F_{11}$/octane) and monophase ($CF_3C_6H_5$) conditions, as will be detailed in a full paper. Of particular novelty and the emphasis of this communication is the thermomorphic[10] behavior shown in Figure 1. Between 20−80 and 20−100 °C, 1 exhibits ca. 60- and 150-fold increases of solubility in octane. Although octane is one of the best organic solvents for dissolving nonpolar fluorous compounds, little 1 could be detected at 0 °C by GC (0.31 mM) or ^{31}P NMR. At 20 °C, millimolar concentration levels were present (1.13 mM, GC; 0.97 mM, NMR). A distinct jump in solubility was observed near the melting point (19.6 mM, 50 °C), followed by continued increases (63.4 mM, 80 °C; 157 mM, 100 °C).

Such a dramatic solubility/temperature dependence suggests an obvious catalyst recycling method. As shown in Chart 2, 1 (0.1 equiv), 2a (2.0 equiv), and 3 were combined in octane (65.0 mM in 3). The sample was kept at 65 °C (8 h) and cooled to −30 °C (arbitrary temperature of a convenient freezer). The precipitated catalyst (in some cases orange-colored) was isolated by decantation. GC analysis of the supernatant indicated a 82%

(1) (a) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641. (b) Cavazzini, M.; Montanari, F.; Pozzi, G.; Quici, S. *J. Fluorine Chem.* **1999**, *94*, 183. (c) Bhattacharyya, P.; Croxtall, B.; Fawcett, J.; Fawcett, J.; Gudmunsen, D.; Hope, E. G.; Kemmitt, R. D. W.; Paige, D. R.; Russell, D. R.; Stuart, A. M.; Wood, D. R. W. *J. Fluorine Chem.* **2000**, *101*, 247.

(2) Full papers with extensive literature background: (a) Horváth, I. T.; Kiss, G.; Cook, R. A.; Bond, J. E.; Stevens, P. A.; Rábai, J.; Mozeleski, E. J. *J. Am. Chem. Soc.* **1998**, *120*, 3133. (b) Juliette, J. J. J.; Rutherford, D.; Horváth, I. T.; Gladysz, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 2696. (c) Richter, B.; Spek, A. L.; van Koten, G.; Deelman, B.-J. *J. Am. Chem. Soc.* **2000**, *122*, 3945. (d) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866.

(3) Survey of practical considerations and underlying physical principles: Barthel-Rosa, L. P.; Gladysz, J. A. *Coord. Chem. Rev.* **1999**, *190−192*, 587.

(4) For an essay on the "ideal recoverable catalyst", see: Gladysz, J. A. *Pure Appl. Chem.* **2001**, *73*, 1319.

(5) Alvey, L. J.; Rutherford, D.; Juliette, J. J. J.; Gladysz, J. A. *J. Org. Chem.* **1998**, *63*, 6302.

(6) (a) Alvey, L. J.; Meier, R.; Soós, T.; Bernatis, P.; Gladysz, J. A. *Eur. J. Inorg. Chem.* **2000**, 1975. (b) Klose, A.; Gladysz, J. A. *Tetrahedron Asymmetry* **1999**, *10*, 2665. (c) Soós, T.; Bennett, B. L.; Rutherford, D.; Barthel-Rosa, L. P.; Gladysz, J. A. *Organometallics* **2001**, *20*, 3079. (d) Jiao, H.; Soós, T.; Meier, R.; Le Stang, S.; Rademacher, P.; Kowski, K.; Jafarpour, L.; Hamard, J.-B.; Nolan, S. P.; Gladysz, J. A. submitted to *J. Am. Chem. Soc.*

(7) The Bayliss−Hillman reaction is one extensively studied example. See: (a) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (c) Vedejs, E.; Daugulis, O.; Mackay, J. A.; Rozners, E. *Synlett* **2001**, 1499.

(8) (a) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241. (b) R. Meier, Ph.D. Thesis, Universität Dortmund, 1998.

(9) Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Curran, D. P. *Top. Curr. Chem.* **1999**, *206*, 79.

(10) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058 and references therein.

10.1021/ja011444d CCC: $20.00
Published on Web 10/27/2001

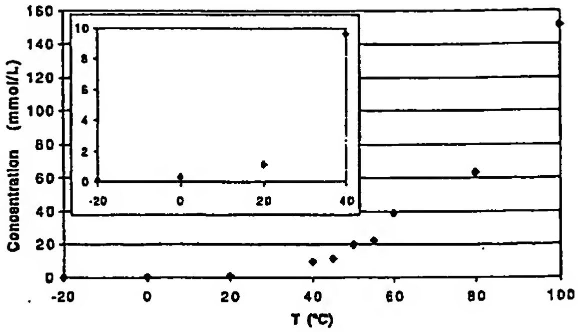


Figure 1. Temperature-dependent solubility of $P((CH_2)_2(CF_2)_7CF_3)_3$ (**1**) in octane (GC vs internal standard; ≥15 min stirring at each temperature and ≥5 min settling period with no stirring).

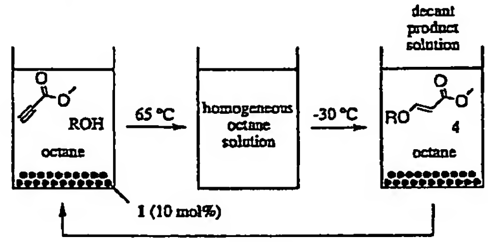
yield of **4a**. The recovered catalyst was used for four further cycles without deterioration in yield, as summarized in Chart 2. Similar results were obtained with alcohols **2b-d**. No background reactions were detected at 65 °C in the absence of **1**, and rates were much slower at lower temperatures.

In a procedural variation, identical reactions were conducted in the presence of Teflon beads or shavings. This provided an adsorbant for the precipitated catalyst, and physically facilitated recycling. The Teflon/catalyst residue from such an experiment (synthesis of **4a**) was extracted with $CF_3C_6H_5$, and a known amount of PPh_3 was added. A ^{31}P NMR spectrum indicated a 89.5% recovery of **1** and 7.8% of two new phosphorus-containing species (possibly educt-derived alternative rest states). The octane solution of the product showed a barely integratable signal for the oxide of **1** (0.4% leaching).[5]

In a further refinement, **2a** and **3** were reacted as in Chart 2, but in the absence of solvent. Toluene was added to efficiently separate **4a** from solid **1**, which was then reused. Yields for a four-cycle sequence were 99, >99, 97, and 95%. The temperature dependence of the solubility of **1** in toluene was also probed. At 0 and 20 °C, concentrations were similar to those in octane. However, solubilities were reduced by half at 40 and 45 °C (4.00 and 5.56 mM), and rose to only 14.4 M at 80 °C. We view this as a logical consequence of the higher solvent polarity and speculate that more dramatic gradients can be achieved with shorter pony tails.

We believe that one-solvent protocols of the type described above will be applicable to a wide variety of fluorous catalysts. It is probably not always necessary to traverse a melting point to achieve a sufficient solubility gradient. Nonetheless, one would expect that the melting points of fluorous compounds can be engineered by shortening, lengthening, or branching the pony tails and by increasing/decreasing their numbers. The phase properties

Chart 2. Fluorous Catalyst Recycling Based upon Liquid/Solid Phase Separation



ROH (2.0 equiv)[a]	Cycle	Yield (%)
2a	1	82
	2	82
	3	80
	4	81
	5	75
2b	1	77
	2	84
	3	71
2c	1	90
	2	86
	3	75
2d	1	79
	2	84
	3	66

[a] Starting concentration of **2**: 1.25 M; reaction time: 8 h; reaction temperature: 65 °C.

of a catalyst family could be optimized and tailored to a broad portfolio of solvents. However, it must be emphasized that the solubility characteristics of the *catalyst rest state*—not the catalyst precursor—are critical for recycling. In Charts 1 and 2, phosphine **1** represents the dominant rest state, but transition-metal catalyst precursors often exhibit induction periods or are otherwise transformed under reaction conditions. In any event, we have unequivocally shown that fluorous catalysts can be utilized under one-phase conditions in ordinary organic solvents and recovered by low-temperature liquid/solid-phase separation[11] and without recourse to fluorous solvents. There are obvious further refinements of our methodology, and these will be reported in due course.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (DFG; GL 300-3/1) for support (liquid/liquid biphase experiments).

JA011444D

(11) For a complementary approach to designing liquid/solid-phase separations, see: Bosanac, T.; Yang, J.; Wilcox, C. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1875; *Angew. Chem.* **2001**, *113*, 1927.

APPENDIX B

Katalyse: MW 107 / TFT, 65°C, GB   MW 184

~ MW 181, aber 1S erst nach Extraktion mit ~~Oct~~ Octane zugeben (zur ~~Kat~~ Oct.-Lsg.)

Problem: Kat fällt als Suspension aus → z.T. mit Spritze entfernt → Teflon-Stückchen → etwas besser

Zyklen:

1) Meprop: 40,5 mg (0,4817 mmol), 1S: 53,6 mg (0,3429 mmol)
n(Prod) = 0,435 mmol ≙ 90,3%

2) ~~44,4~~ 45,0 mg (0,~~4936~~ 5353 mmol) 51,6 (0,3301 -)
0,529 98,8%

3) 42,3 (0,5032 mmol) 53,9 (0,3448 -)
0,477 94,8%

4) 45,0 (0,5353 -) 51,3 (0,3282 -)
0,520 97,1%

5) 44,4 (0,5281 -) 52,9 (0,3384 -)
0,495 93,8%

Testlt - Cat. Recovery : MW 107 / 65°C, Octan, GB MW 188

Standard-Ansatz (68,0 mg Kat. ≙ 0,04955 mmol), 8 h in Octan, ~~...~~ bei 65°C, dann Teflon drehen, RT, mit Spritze + Filter org. Phase entfernen (kein Tol!),

I, mit PPh_3 / TFT-Lsg (2 ml, 41,04 mg ≙ 0,1564 mmol, aus Stammlsg) auswaschen, C_6D_6 dazu → NMR

	auf 100 %:
⇒ 0,04433 mmol Kat ≙ 89,5 %	91,6
Fest bei + 44,4 ppm : 2,768 µmol ≙ 5,6 %	5,7
34,4 - : 1,075 - ≙ 2,2 %	2,3

97,3 %

II, org. Phase:

zu orga. Phase 130,5 mg (≙ 8,8051 µmol PPh_3) eine Lsg v. 63,6 mg (0,2425 mmol) PPh_3 in 3530,2 mg TFT + etw. C_6D_6 geben, NMR

⇒ + 41,9 ppm : 0,186 µmol ≙ 0,4 % | 0,4

100,0

Σ 97,7 % ges

APPENDIX C

Stand: 30.07.2001

!! REVISED !!

JAG ARBEITSKREIS/GROUP
TREFFEN/MEETINGS
Winter/Summer Semester 2001
Wednesdays 09:00-10:30 unless noted

03-January	no meeting
10-January	no meeting
17-January	SFB activities (also 16-January)
24-January	Dr. Sylvie LeStang
31-January	Dr. Haijun Jiao
07-February	Dr. Tibor Sóos
14-February	Mr. Wolfgang Mohr
21-February	Hirschegg Graduiertenkolleg meeting
28-February	Ms. Charlotte Emnet
07-March	Prof. Greg Grant
14-March	Mr. Eike Bauer
21-March	Mr. Marc Wende
28-March	Mr. Jürgen Stahl
04-April	no meeting
11-April	Mr. Long Dinh
18-April	Rennes Expedition
25-April	Mr. Olivier Delacroix
02-May	no meeting
09-May	Dr. Wojciech Jaunky (Strassbourg research)
16-May	no meeting
23-May	Ms. Sandra Eichenseher
30-May	Mr. Christophe Jardin
06-June	Mr. Qinglin Zheng
13-June	no meeting
20-June	Prof. Gladysz
27-June	Prof. Gladysz
04-July	Prof. Gladysz
11-July	Prof. Gladysz
18-July	Mr. Jürgen Betz
25-July	Dr. Moris Eisen (Israel research)
01-August	no meeting
08-August	Dr. Frank Stahl
15-August	Prof. Gladysz
22-August	Ms. Berta Perez